



17293 DIV

**PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of )  
Massaro et al. ) Examiner: D. Margaret  
Serial No.: 09/919,195 ) Seaman  
Filed: July 31, 2001 ) Art Unit: 1625  
For: METHODS AND COMPOSITIONS FOR )  
THE TREATMENT AND PREVENTION )  
OF LUNG DISEASE )

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Appeal Brief  
Gabor L. Szekeres

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Date:

November 12, 2004

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Appeal Brief

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE =  
BEFORE THE BOARD OF APPEALS

APPELLANT'S BRIEF PURSUANT TO CONSOLIDATED PATENT  
RULES § 41.37

Honorable Commissioner of Patents  
P.O.Box 1450  
Alexandria, VA 22313-1450

In accordance with Consolidated Patent Rules 41.37 Appellant hereby submits its Brief on Appeal together with the fee in the amount of \$ 340 as required by § 41.20(b)(2) and Request for Extension of Time of two months, pursuant to § 1.136 together with a large entity fee of \$ 430.

**Real Party in Interest [§ 41.37(c)(1)(i)]**

The real parties in interest are:

Allergan Inc. 2525 Dupont Drive, Irvine California 92612 by virtue of assignment recorded on Reel/Frame 013898/0170 in the United States Patent and Trademark Office, and

Concurrent Pharmaceuticals Inc. 502 West Office Center Drive Fort Washington Pennsylvania 19034 by virtue of license from Allergan Inc.

**Related Appeals and Interferences [§ 41.37(c)(1)(ii)]**

There are no related appeals nor interferences.

**Status of Claims [§ 41.37(c)(1)(iii)]**

Claims 13 through 28 are pending and on appeal. Claims 29 and 30 were canceled in a preliminary amendment dated July 30, 2001. The subject

matter of Claims 29 and 30 was patented in United States Patent No. 6,303,648, issued on October 16, 2001.

Claims 1 – 12 of the application were canceled during prosecution, in an amendment dated August 16, 2002.

#### **Status of Amendments [§ 41.37(c)(1)(iv)]**

No amendment was filed after the final rejection of Claims 13 through 28, dated February 17, 2004. All amendments filed before the final rejection have been entered and comprise the record on this appeal.

#### **Summary of Claimed Subject Matter [§ 41.37(c)(1) (v)]**

The claimed subject matter of independent Claim 13 is a method of treatment or prevention of alveolar destruction (a form of lung disease) of a mammal by administering to the mammal a therapeutically effective amount of a compound which is an *antagonist* of retinoid receptors of the RAR  $\beta$  type, does not modulate RXR receptors and not specific to at least one other RAR receptor subtype (namely not specific to at least one of the RAR  $\alpha$  and RAR  $\gamma$  subtypes. (see page 4 line 26 through page 5 line 24; page 11 lines 1 - 6.)

Dependent Claims 14 through 20 are more specific, and have additional inventive features (limitations) as follows:

In Claim 14 the RAR  $\beta$  antagonist is defined as not specific to RAR  $\alpha$  receptors. (page 5, lines 2 – 6; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 15 the RAR  $\beta$  antagonist is defined as not specific to RAR  $\gamma$  receptors. (page 5, lines 6 – 10; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 16 the RAR  $\beta$  antagonist is defined as not specific to either RAR  $\alpha$  or to RAR  $\gamma$  receptors. (page 5, lines 10 – 14; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 17 the RAR  $\beta$  antagonist is administered in the form of an inhalant. (page 12, lines 9 – 15; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 18 the inhalant contains RAR  $\beta$  antagonist which is not specific to RAR  $\alpha$  receptors. (page 24, originally filed Claim 18; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 19 the inhalant contains RAR  $\beta$  antagonist which is not specific to RAR  $\gamma$  receptors. (page 24, originally filed Claim 19; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 20 the inhalant contains RAR  $\beta$  antagonist which is not specific to either RAR  $\alpha$  or to RAR  $\gamma$  receptors. (page 24, originally filed Claim 20; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

The claimed subject matter of independent Claim 21 is a method of increasing the gas-exchange surface area of a mammalian lung by administering to the mammal a therapeutically effective amount of a compound which is an *antagonist* of retinoid receptors of the RAR  $\beta$  type and has specific RAR modulating activity. (see page 4, lines 26 through

page 5 line 2; page 5 line 17 – 24; page 17 line 22 through page 21 line 6; page 24 originally filed Claim 21).

Dependent Claims 22 through 28 are more specific, and have additional inventive features (limitations) as follows:

In Claim 22 the RAR  $\beta$  antagonist is defined as not specific to RAR  $\alpha$  receptors. (page 5, lines 2 – 6; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 23 the RAR  $\beta$  antagonist is defined as not specific to RAR  $\gamma$  receptors. (page 5, lines 6 – 10; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 24 the RAR  $\beta$  antagonist is defined as not specific to either RAR  $\alpha$  or to RAR  $\gamma$  receptors. (page 5, lines 10 – 14; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 25 the RAR  $\beta$  antagonist is administered in the form of an inhalant. (page 12, lines 9 – 15; page 9 line 26 through page 10 line 6).

In Claim 26 the inhalant contains RAR  $\beta$  antagonist which is not specific to RAR  $\alpha$  receptors. (page 25, originally filed Claim 26; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 27 the inhalant contains RAR  $\beta$  antagonist which is not specific to RAR  $\gamma$  receptors. (page 25, originally filed Claim 27; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

In Claim 28 the inhalant contains RAR  $\beta$  antagonist which is not specific to either RAR  $\alpha$  or to RAR  $\gamma$  receptors. (page 25, originally filed Claim 20; page 9 line 26 through page 10 line 6; page 11 lines 7 - 18).

**Grounds of Rejection to be Reviewed on Appeal** [§ 41.37(c)(1)(vi)]

**First ground:** The Examiner rejected all pending claims pursuant to 35 U.S.C. § 112, first paragraph. In this rejection the Examiner did not make any distinction among the pending claims. On pages 2 – 6 of the final Office Action of February 17, 2004 the Examiner discussed an alleged “failure to comply with the written description requirement” (page 2 second numbered paragraph of the final Office Action) and thereafter separately an alleged failure to provide a “specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention”. (page 3 third numbered paragraph of the final office Action). Applicant is of the view and urges that the requirement to provide a “written description” is the same as the requirement for an enabling disclosure. Therefore, these two allegedly separate grounds of rejection in the final Office Action are the same and can be discussed together.

In applicant’s view with respect to the rejection pursuant to 35 U.S.C. § 112, first paragraph, applicant believes that all pending claims can be discussed as a group. The essence of the rejection is that the compounds used in the method are defined by the biological/pharmaceutical properties,

namely that they need to be antagonists of RAR  $\beta$  receptors, and more specifically in the preferred embodiment that they should not be modulators of RAR  $\alpha$  receptors, or of RAR  $\gamma$  receptors. The Examiner made this ground of the rejection on the basis that there is no chemical structural limitation set forth for the compounds having such biological/pharmacological activity. It is true that in the instant claims there is no structural limitation for the compounds which can be used in the method. However, as it is explained in more detail in the “arguments” below, applicant is of the view that the description of the required biological/pharmacological properties is sufficient as an enabling disclosure. Therefore the ultimate holding of insufficient disclosure is in serious error.

**Second ground:** All pending claims were rejected pursuant to 35 U.S.C. § 102 as being anticipated by each of the following references:

*Yu* CA 112:230122, abstract 1990;  
*Song* Proc. Natl. Acad. Sci, USA Vol 91, pp 10809-10813, 1994;  
*Wu* The EMBO Journal, Vol 16(7), pp 1656 – 1669, 1997;  
*Xu* CA 127::16087, abstract 1997;  
*Cong* American Journal of Physiology, 275(2, pt.1) L239-L246, 1998;  
*Ghaffari* American Journal of Physiology, 276(3, pt.1) L398-L404, 1999.

The Examiner stated as grounds of the rejection that *Ghaffari* discloses compounds that cause modulation of RAR receptors (called “RAR modulation” in the final Office action); *Cong* discloses RAR modulation having a role in the development of the lung, and that the remaining

references also teach RAR modulation in lung tissue. (see page 7 of the final Office Action of February 17, 2004). The Examiner's position appears to be (and for a holding of anticipation logically must be) that each of these references disclose within their "four corners" all elements of the claimed invention, expressly or inherently. For the reasons stated in the "argument" below, this position is in serious error.

In applicant's view, with respect to the rejection pursuant to 35 U.S.C. § 102 the claims should be divided in at six separate groups of inventiveness and the erroneous nature of this rejection merits discussion with respect to each group.

**Argument [§ 41.37(c)(1)(vii)]**

**Rejection Pursuant to 35 U.S.C. § 112, first paragraph; All Pending Claims Discussed as a Group**

The Examiner asserts that the disclosure is insufficient and not enabling to a person of ordinary skill in the art "because the scope of the claims is unknown due to the *structure limitations* not being specifically disclosed." (page 2 of the final Office Action of February 17, 2004, italics added). This assertion is in serious error because there is no requirement in patent law that the chemical structure of a claimed group of compounds must be disclosed. It is well established law that a person of ordinary skill in the art *can be enabled* by describing the physical or biological properties of a class of compounds which are used in a claimed

method. As it will become apparent below, this requirement is satisfied in connection with the instant claims.

The Examiner stated that,

“the claimed invention invention is drawn to compositions that have RAR $\beta$  antagonist having specific RAR modulating activity and a method of of treating using such compositions. However, the only compounds that are enabled by the instant specification have already been patented.” (Page 3 of the final Office Action)

The just quoted statement from the final Office Action that rejects the claims pursuant to 35 U.S.C. § 112, first paragraph is indicative that the Examiner has confused the requirements for patenting new compositions and patenting methods using old compositions. The law is well established that a new and unobvious use of an old composition is patentable. The statement is grossly in error because the instant claims are not drawn to compositions. They are drawn only to methods of treatment.

The Examiner also stated that,

“The only compounds that fit within the bounds of the instant claim 13 are the compounds/methods of the US Patent #6,303,648. The instant specification does not have written description as to how to make compounds that fit within the instant parameters outside the compounds of the parent patent.” (page 3 of the final Office Action)

The just quoted statement in the final Office Action also reveals a serious misconception or misreading of the instant disclosure. On page 12 line 30 through page 13 line 8 the instant specification teaches that the “synthesis of candidate compounds having specific RAR modulating activity is well known in the art”. The term “*specific RAR modulating activity*” is defined on page 5 lines 17 – 24. The essence of this definition is that compounds having “specific RAR modulating activity” bind at least ten times better to RAR receptors than to RXR receptors. Page 5 line 25 through page 6 line 6 briefly describe the assay or method by which the “specific RAR modulating activity” of a compound can be *routinely* determined, and incorporates by reference the disclosures (U. S. Patent No. 5,776,699 and PCT Publication No. W093/11755) where the nature of the required assays is described in precise detail. Still further, on page 13 line 9 through page 14 line 20 the specification again describes, and in more detail, routine assays for determining “specific RAR modulating activity” and routine assays for measuring the dissociation constant (Kd) of a given ligand with retinoid receptors. This part of the specification again refers to and incorporates by reference United States Patent Nos. 5,455,265 and 5,776,699.

Moreover, the passage on Page 12 line 30 through page 13 line 8 of the instant specification incorporates by reference U.S. Patent Nos. 5,739,338; 5,728,846; 5,760,276 and 5,877,207 each of which describes “the synthesis of RAR ligands having antagonist and/or inverse agonist activity.

These patents have general formulas of broad scope and also list numerous exemplary compounds of specific disclosed structure.

Therefore, the statement in the final Office Action that “The only compounds that fit within the bounds of the instant claim 13 are the compounds/methods of the US Patent #6,303,648”, while technically may be correct, is a misstatement in context, because with the numerous structures of broad scope and the numerous specific examples of the patents incorporated by reference the instant specification teaches a large number of compounds usable in the present invention, or suitable for undergoing the routine assays for “specific RAR modulating activity” and for specific or selective RAR $\beta$  antagonist activity.

The Examiner refers to the factors of *in re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (fed. Cir. 1988). Applicant urges that the factors of enablement in *in re Wands* “are illustrative, not mandatory. What is relevant depends on the facts.” *Enzo Biochem Inc. v. Calgene Inc.*, 52 USPQ2d 1129 (Fed. Cir. 1999).

Nevertheless, even applying the *Wands* factors the holding of a lack of enablement is in serious error. Specifically, the claims are broad but the nature of the invention is commensurately broad in that the applicant discovered that antagonists of RAR $\beta$  retinoid receptors which do not have significant RXR modulating activity, and preferably have no RAR $\alpha$  nor RAR $\gamma$  modulating activity, are suitable to be used for curing or preventing certain lung diseases or deficiencies in mammals. The state of the prior art and the level of skill in the art are such, as evidenced by the patents

incorporated by reference, that a person of ordinary skill can routinely screen compounds for their above-noted biological/physiological profile. In the specification Applicant provides clear and routine methods of screening as directions for determining the suitability of any compound for use in the method of the present invention. The specification provides one exemplary compound of specific structure as a working example but the compounds incorporated by reference provide a multitude of additional working examples. Finally, the experimentation needed for determining the suitability of a compound to be used in the methods of the invention is mere routine experimentation easily performed by persons who have ordinary but nevertheless high skill in the art. Such routine testing or assaying should not be considered undue experimentation especially in view of the fact that the prior art includes hundreds of patents describing compounds which have retinoid receptor modulating activity and are therefore candidates to be screened for the required “specific RAR modulating” and RAR $\beta$  antagonist properties.

In a previous Office Action the Examiner stated that there is no direction in the specification for a person of ordinary skill in the art what compounds to screen for the required biological/pharmacological activity of the compounds used in the instant invention. Therefore, in the Examiner’s view, aspirin is as likely to be tested as any other drug. Page 5 of the Office Action of September 15, 2003) This observation, or ground of the rejection is in serious error for the following reasons. A multitude of compounds are described and/or known in the pharmaceutical arts to be modulators of

retinoid receptors (retinoids). Persons of ordinary skill in the art tend to be scientists with advanced degrees who are likely to be aware of the “retinoid receptor modulating” nature of a compound and are likely to screen only such compounds. They are highly unlikely to screen aspirin.

In the final Office Action the Examiner states the additional reason for the “lack of enablement” rejection,

“Furthermore, no information is presented as to how the undisclosed antagonist compound would have been administered to treat an unspecified disease. Thus, the skilled artisan would not have been able to practice the steps required by the claimed invention.” (Page 6 of the final Office Action)

The just quoted passage in the final Office Action is in error. On page 11 line 21 through page 12 line 29 the specification teaches that medical conditions such as emphysema and BPD (brochopulmonary dysplasia) can be treated in accordance with the present invention. This section of the specification also describes modes of administration, for example as an inhalant, or a composition suitable for systemic administration (intravenous and/or intraperitoneal). Pharmacological vehicles for all these methods of administration are well known in the art. (see page 12 lines 16 – 29).

In view of the novel and unobvious discovery that compounds having “specific RAR modulating” and RAR $\beta$  antagonist properties are useful for treating or preventing certain lung disorders, the multitude of prior art “retinoid compounds” provide a multitude of exemplary compounds to be subjected to the routine assays described in the instant specification to obtain

a multitude of compounds suitable to be used in the novel method of the invention.

In light of the foregoing the rejection of all pending claims for a lack of adequate written description and/or lack of enabling disclosure is in serious error and should be reversed.

Rejection Pursuant to 35 U.S.C. § 102; Claims Discussed in Six Separate Groups

Comments Applicable to All Claims:

The grounds provided in the final Office Action and in the previous Office Actions for rejecting the claims as “anticipated” by each of the cited references is insufficiently explained, and is in serious error.

In response to the Section 102 rejection in a preceding Office Action based on these references, applicant requested the Examiner to explain:

“If the Examiner has found an anticipatory disclosure of each and every limitation of any of the present claims in one or more of these references, Applicants respectfully request the Examiner to expressly point to such disclosure.” (Reply and Amendment of August 14, 2003, page 6).

The law is well settled that an allegedly anticipatory disclosure must disclose each and every limitation of the allegedly anticipated patent claim. Applicant urges that none of these allegedly “anticipatory” references satisfy the legal requirement for anticipation and that the Examiner has never responded adequately to the just quoted request by the applicant.

Claim Group 1, Claims 13 – 16

As noted above these claims require in the method of treatment or prevention the use of a compound that is an RAR $\beta$  antagonist, and not a modulator of RXR receptors. (see the definition of “specific RAR modulating activity” on page 5 lines 17 – 24 of the specification.) nor a modulator of either RAR $\alpha$  or RAR $\gamma$  receptors. None of the cited references disclose all these elements or limitations. The Examiner asserts that these elements must be inherent in the compounds used in the references. For the reason explained below the assertion of inherency is in serious error.

There is a significant difference between just being a “retinoid”, namely a compound having some modulating activity on any or all retinoid receptors, and being selective to RAR receptors (not active on RXR receptors) and then being further selective by acting as an *antagonist* of RAR $\beta$  and being inactive on either RAR $\alpha$  or RAR $\gamma$  receptors. These distinctions or limitations of the instant claims are not expressly found in the references.

On page 2 lines 26 through page 3 line 29 the instant specification points out the well known fact that all *trans* retinoic acid (ATRA) has beneficial effect on mammals having destroyed or insufficient alveoli, by reversing the destruction and/or promoting formation of more alveoli. ATRA is a well known agonist, not an antagonist of all RAR receptors. Moreover,

“the retinoid receptors, when bound by an appropriate ligand, are mediators of various life processes, including reproduction, metabolism, differentiation, hematopoiesis and embryogenesis.” (page 3 lines 17 – 21)

Therefore, there is room, in fact a need, in the art for drugs, such as the ones used in the instant method, which tend to be more selective, treat lung diseases by promoting alveoli formation without a high likelihood of serious side effects.

It should also be noted that because ATRA is an agonist of all three RAR receptors it is a quite different and a surprising discovery of the present invention that a RAR $\beta$  antagonist also has a like effect on mammalian lungs without a high likelihood of the serious side effects that administration of ATRA may cause.

#### Claim Group 2, Claims 17 – 20

In addition to the features and elements discussed above, these claims require that the RAR $\beta$  antagonist compound should be administered as an *inhalant*. The comments made above with respect to Claims 13 – 16 are fully applicable here, with the further comment that no cited reference includes *all the limitations*, including the call for an “inhalant” of these claims.

As with respect to all claims it is emphasized again that being a “retinoid” or a modulator of “retinoid receptors” is not the same as being an antagonist of RAR $\beta$  and having no modulating activity on RXR receptors.

### Claim Group 3, Claim 21

Claim 21 requires the use of an RAR $\beta$  *antagonist* which is not a modulator of RXR receptors (see the definition of “specific RAR modulating activity” on page 5 lines 17 – 24 of the specification) to increase the gas-exchange surface area of a mammalian lung.

Although this claim does not

require the antagonist to be inactive with regard to RAR $\alpha$  or RAR $\gamma$  receptors, for the reasons explained above the combination of the features or limitations recited in the claim are not present in any of the cited references, neither expressly nor inherently.

As with respect to all claims it is emphasized again that being a “retinoid” or a modulator of “retinoid receptors” is not the same as being an antagonist of RAR $\beta$  and having no modulating activity on RXR receptors.

### Claim Group 4, Claims 22 – 24

In addition to all features or limitations in Claim 21, these claims also have the requirement that the compound used in the treatment to increase gas-exchange surface area in the mammalian lung should be inactive as a modulator of either the RAR $\alpha$  or RAR $\gamma$  receptors. For the reasons explained above the combination of the features or limitations recited in this claim are not present in any of the cited references, neither expressly nor inherently.

As with respect to all claims it is emphasized again that being a “retinoid” or a modulator of “retinoid receptors” is not the same as being an antagonist of RAR $\beta$  and having no modulating activity on RXR receptors.

Claim Group 5, Claim 25

Claim 25 requires the use of an RAR $\beta$  *antagonist* which is not a modulator of RXR receptors (see the definition of “specific RAR modulating activity on page 5 lines 17 – 24 of the specification) in an *inhalant* to increase the gas-exchange surface area of a mammalian lung.

Although this claim does not require the antagonist to be inactive with regard to RAR $\alpha$  or RAR $\gamma$  receptors, for the reasons explained above the combination of the features or limitations recited in the claim are not present in any of the cited references, neither expressly nor inherently.

As with respect to all claims it is emphasized again that being a “retinoid” or a modulator of “retinoid receptors” is not the same as being an antagonist of RAR $\beta$  and having no modulating activity on RXR receptors.

Claim Group 6, Claims 22 – 24

In addition to all features or limitations in Claim 25 that calls for an *inhalant*, these claims also have the requirement that the compound used in the treatment to increase gas-exchange surface area

in the mammalian lung should be inactive as a modulator of either the RAR $\alpha$  or RAR $\gamma$  receptors. For the reasons explained above the combination of the features or limitations recited in this claim are not present in any of the cited references, neither expressly nor inherently.

As with respect to all claims it is emphasized again that being a "retinoid" or a modulator of "retinoid receptors" is not the same as being an antagonist of RAR $\beta$  and having no modulating activity on RXR receptors.

In light of all of the foregoing the rejection of Claims 13 – 28 of the above-identified application is in error and should be reversed.

Respectfully submitted

Date: Nov. 12, 2004

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APPENDIX  
CLAIMS ON APPEAL

13. A method for the treatment or prevention of alveolar destruction in a mammal comprising the step of administering a therapeutically effective amount of an RAR $\beta$  antagonist having specific RAR modulating activity to said mammal, and such antagonist is not specific to at least one other RAR receptor subtype.
14. The method of claim 13, wherein said RAR $\beta$  antagonist is not specific to RAR $\alpha$ .
15. The method of claim 13 wherein said RAR $\beta$  antagonists is not specific to RAR $\gamma$ .
16. The method of claim 13 wherein said RAR $\beta$  antagonist is not specific to RAR $\alpha$  or RAR $\gamma$ .
17. The method of claim 13 wherein said composition is administered in the form of an inhalant.
18. The method of claim 17 wherein said RAR $\beta$  antagonist is not specific to RAR $\alpha$ .
19. The method of claim 17 wherein said RAR $\beta$  antagonist is not specific to RAR $\gamma$ .
20. The method of claim 17 wherein said RAR $\beta$  antagonist is not specific to RAR $\alpha$  or RAR $\gamma$ .

21. A method to increase the gas-exchange surface area of a mammalian lung in a mammal in need thereof comprising the step of administering a therapeutically effective amount of an RAR $\beta$  antagonist having specific RAR modulating activity to said mammal.
22. The method of claim 21, wherein said RAR $\beta$  antagonist is not specific to RAR $\alpha$ .
23. The method of claim 21 wherein said RAR $\beta$  antagonist is not specific to RAR $\gamma$ .
24. The method of claim 21 wherein said RAR $\beta$  antagonist is not specific to RAR $\alpha$  or RAR $\gamma$ .
25. The method of claim 21 wherein said composition is administered in the form of an inhalant.
26. The method of claim 25, wherein said RAR $\beta$  antagonist is not specific to RAR $\alpha$ .
27. The method of claim 25 wherein said RAR $\beta$  antagonist is not specific to RAR $\gamma$ .
28. The method of claim 25 wherein said RAR $\beta$  antagonist is not specific to RAR $\alpha$  or RAR $\gamma$ .